

# Mg

DIABETES MELLITUS DIABETES

## Diabetes Mellitus and Magnesium: *Unlikely Partners*



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# Introduction

Scientists and clinicians are becoming increasingly aware of the critical role magnesium plays in diabetes mellitus (DM). A deficiency of this mineral, which is involved in more than 300 enzymatic reactions throughout the body, would be expected to negatively impact essential biochemical processes. Insulin secretion and action, for example, depend on adequate cellular magnesium. Polyuria—a characteristic of the hyperglycemic state of DM—results in a significant amount of magnesium being excreted in the urine, leading to total-body magnesium deficiency. Experimental and clinical studies have demonstrated significant associations between decreased magnesium levels and increased insulin resistance as well as increased severity of DM complications. Magnesium supplementation can be an effective, safe and inexpensive way to insure adequate magnesium status for DM patients.

The term *diabetes mellitus*, derived from the Greek words meaning *siphon* and *sweet*, refers to a group of metabolic disorders characterized by elevated blood glucose resulting from inadequate insulin secretion or insulin action. In some cases the primary defect is the synthesis, release or action of insulin; in other instances a metabolic defect beyond insulin is responsible. The chronic hyperglycemia that results may eventually lead to dysfunction, damage and eventual failure of various organ systems, especially the heart, kidneys, blood vessels, nerves and eyes. Because the primary symptoms typically include polyuria, polydipsia and polyphagia, the early descriptions of DM referred to this disease as the “great pissing evil.” Secondary symptoms associated with a defect in glucose homeostasis include fatigue, susceptibility to infections, impaired growth and blurred vision.

Although most health care providers primarily associate DM with abnormal carbohydrate metabolism, protein and lipid metabolism are also adversely affected by the inadequate insulin secretion or decreased tissue responsiveness to insulin (insulin resistance). The tissue damage that results from glycosylation of various proteins and the accumulation of polyols produced from chronically elevated glucose levels are believed to contribute to the

early development of atherosclerosis, cataracts, cerebrovascular disease and neuropathies. DM's long-term microvascular and macrovascular complications account for the tremendous morbidity and resultant health care costs associated with DM patient care.

In the United States it has been estimated that more than 16 million people (5.9% of the population) have one of the various forms of DM, and of these individuals approximately one-third are unaware that they have the disease. Men and women appear to be equally affected; however, minority groups such as African Americans, Asians and Latinos have a disproportionately higher rate of DM.<sup>1</sup> In 1997, the costs associated with DM in the United States were approximately \$100 billion. The direct health care costs were \$44 billion, a value that represented approximately 6% of the total annual health care expenditures. Lost productivity in school and at work accounted for an additional \$54 billion of indirect costs. In the year 2000, the costs associated with DM continue to escalate.

# Diabetes Mellitus and Magnesium: Unlikely Partners

## Classifications of Diabetes Mellitus

Recently the American Diabetes Association, delineated DM into categories including type 1, type 2, gestational and several others.<sup>2</sup> Type 1 DM is typically a result of an autoimmune-mediated process in which pancreatic beta-cells in the Islets of Langerhans are destroyed resulting in little if any insulin production. Previously, this form of DM was called juvenile-onset or insulin-dependent DM (IDDM). The most prevalent form of DM is type 2, previously called maturity-onset or non-insulin-dependent DM (NIDDM), and is generally characterized by insulin resistance. Although type 2 DM may be associated with some degree of an insulin secretion defect, patients are often overweight and do not usually have evidence of circulating autoantibodies against the pancreatic beta-cells. Other forms of DM include gestational, iatrogenic (e.g., corticosteroids, thiazides, thyroid hormone, beta-adrenoceptor blockers), endocrinologic (e.g., acromegaly, Cushing's disease, glucagonoma, hyperthyroidism, pheochromocytoma) and many specific genetic defects of beta-cell function or insulin action.

## The Role of Minerals

A growing body of research shows an association between DM and alterations in the homeostasis of several trace minerals. Impaired insulin release, altered insulin action and increased glucose intolerance in experimental

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### Target Audience

Pharmacists, Primary Care Physicians, Physician Assistants, Nurse Practitioners and other healthcare providers.

### Educational Needs Addressed

#### Diabetes Mellitus and Magnesium

Disorders of mineral metabolism are among the less well-understood clinical problems encountered by clinicians, and magnesium deficiency leads that list. Magnesium is one of the most important minerals in the body. It serves as a co-factor in more than 300 bodily reactions. A deficiency of magnesium may lead to a number of serious consequences, such as hypocalcemia, hypokalemia, hyponatremia, and life-threatening arrhythmias. This module is intended to update the reader on the causes of magnesium deficiency, how to prevent the disorder, and how to replace deficits in a safe and effective fashion. The association of magnesium deficiency and diabetes mellitus will be reviewed with specific emphasis on how poorly controlled diabetes leads to a deficiency of magnesium.

### Goal

To review the role of magnesium in health and disease states, with a special emphasis on using this mineral to optimize the action of insulin and alter development of long-term complications of diabetes mellitus.

### Objectives

After completing this lesson the health care provider will be able to:

- Identify nutritional sources of magnesium and describe its role in normal and pathophysiological states, especially diabetes mellitus;

*Continued overleaf*

- Explain the evidence linking suboptimal magnesium status with diabetes mellitus and its associated long-term complications;
- Describe recent studies that use supplemental magnesium as a pharmacotherapeutic adjunct treatment for diabetes mellitus;
- Describe the processes that regulate magnesium's absorption, distribution and excretion; and
- List the side effects and precautions associated with supplemental magnesium use in diabetes mellitus patients.

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animals and human subjects with DM have been linked to a deficit in the cellular availability of magnesium as well as other minerals including chromium, selenium, vanadium and zinc. DM's characteristic polyuria, which results from the glucose-mediated hyperosmotic glomerular filtrate, may be largely responsible for the observed higher-than-normal excretion rates of some of these minerals, especially magnesium. Depending on dietary and supplemental magnesium intake, this enhanced mineral loss may result in a state of negative balance. As a result, there is less magnesium available for optimal insulin secretion or action and this, we expect, would lead to altered, and presumably less-than-optimal, metabolic functioning. In such cases it would be important to correct the altered mineral status by increasing dietary intake of the particular mineral or using supplemental mineral sources. As you will see later in the discussion, many magnesium-rich foods are not optimal for patients with DM. In this case, supplemental magnesium may be the most effective way to insure adequate magnesium levels.

In addition to its involvement in insulin's release and activity, magnesium also plays an important role in other essential biochemical processes. Of significant importance, magnesium is required to activate sodium-potassium adenosine triphosphatase (Na-K ATPase), which maintains electrical gradients across all cell membranes. When hypomagnesemia is present, decreased intracellular potassium distribution can alter cell excitability such as QT-interval prolongation. Magnesium is also an essential cofactor in the action of parathyroid hormone on bone. A magnesium deficiency may result in hypocalcemia, which also can contribute to QT-interval prolongation.

## Tracing the Magnesium-DM Connection

The association between magnesium and diabetes has been known for some time. The earliest suggestion, made in 1952 by Stutzman and Amatuzio, was based on their observation of lower serum magnesium levels in DM patients.<sup>3</sup> Studies in experimental animals demonstrate that magnesium can retard or prevent the induction of insulin resistance and DM, while a magnesium deficit can predispose to hyperglycemia. Based on studies in humans, we can estimate that a significant proportion of patients (25 to 40%) with DM are hypomagnesemic, or have suboptimal magnesium status.<sup>4</sup> In the Atherosclerosis Risk in Communities (ARIC) study, Ma and colleagues investigated the relationship between serum and dietary magnesium and DM.<sup>5</sup> The researchers tested 15,248 subjects and found significantly lower serum magnesium levels in those with DM compared to those without the disease. Researchers also found associations between magnesium levels and both cardio-vascular disease and hypertension, probably as a result of the common biochemical mechanisms underlying the damage observed in each of the diseases. Duplicating the results of the above study, Sasaki and colleagues demonstrated that the DM patients in their study had lower serum levels of ionized magnesium than healthy controls.<sup>6</sup>

In another recent study, researchers examined the serum levels of magnesium in patients with malnutrition-related DM (MR-DM) from Bangladesh.<sup>7</sup> This type of DM is further divided into two categories—fibrocalculus pancreatic diabetes and protein-deficient DM—and constitutes 55% of all patients with DM in Bangladesh. Patients with MR-DM had significantly decreased serum magnesium levels com-

pared with controls or malnourished patients without DM. Almost 70% of those patients with MR-DM had clinically defined hypomagnesemia (serum levels < 0.70 mmol/L) and 90% had hypermagnesuria (urinary magnesium > 335 mmol Mg/mol creatinine). Of the patients who had type 2 DM not related to malnutrition, 42% exhibited hypomagnesemia. The researchers suggested these patients' observed alterations in magnesium status resulted primarily from urinary loss of the mineral associated with an osmotic diuresis, which is characteristic of this disease. Malnutrition, with its associated poor dietary magnesium intake, further contributes to the magnesium deficit in MR-DM patients.

## Magnesium and Diabetes Mortality

Diabetes mellitus is the seventh leading cause of death in the United States. A number of investigations have demonstrated an association between mortality rates among DM patients and the magnesium content of drinking water. One such U.S. study reported a significant negative correlation ( $r=0.56$ ) between the magnesium content of drinking water and the mortality rate of DM patients.<sup>8</sup> Similarly, patients with DM from more than 2,633 different locations in Canada demonstrated a negative correlation between the magnesium content of their drinking water and DM-related mortality rates. Another more recent study illustrated the association between the magnesium content of Taiwanese drinking water and the risk of dying from DM. The authors reported a significant protective effect of magnesium for patients with DM compared to those without the disease. In this study of more than 13,000 subjects,

the odds of dying from DM significantly decreased as the magnesium level in drinking water increased.<sup>9</sup>

## Magnesium and Insulin Action

In support of clinical findings showing an association between hypomagnesemia and the poor glucose control observed in DM patients, numerous studies have demonstrated an important relationship between magnesium and insulin release and activity. The release of insulin caused by a glucose challenge is partly dependent on adequate magnesium. Insulin, via its interaction with ligand-activated tyrosine protein kinase-associated receptors, initiates a cascade of biochemical interactions that result in several physiological, biochemical and molecular events that are involved in carbohydrate, lipid and protein metabolism.<sup>10</sup> Although the binding of insulin to its receptor does not appear to be altered by magnesium status, the ability of insulin once bound to the receptor to activate tyrosine kinase is reduced in hypomagnesemic states.<sup>11</sup> As a result, reduced peripheral glucose uptake and oxidation are often noted in subjects with hypomagnesemia. Decrements in the enzymatic activities of several metabolic pathways are seen in DM patients as a result of the relative magnesium deficiency.<sup>12</sup>

In an animal study involving genetically obese diabetic Zucker rats, magnesium supplementation prevented insulin resistance induced by fructose administration and delayed the onset of insulin resistance and hyperglycemia.<sup>13</sup> In patients with type 2 DM, Yajnik and colleagues found that there was a direct relationship between serum magnesium levels and the efficiency with which glucose was cleared following an intravenous glucose load.<sup>14</sup> Patients with low magnesium levels were much less ef-

ficient at handling a glucose challenge. Similarly, insulin-induced magnesium accumulation by erythrocytes from patients with type 2 DM is markedly impaired and correlates well with the poor insulin-induced glucose disposal observed in these patients.<sup>15</sup>

In a double-blind, randomized, crossover study, Paolisso and colleagues investigated the effects of magnesium supplementation in elderly subjects (average age was 78 years) with insulin resistance on the handling of glucose following an intravenous glucose load and an euglycemic hyperinsulinemic glucose clamp procedure. They also determined the effects of magnesium on erythrocyte magnesium content, which had been shown to be depressed, and membrane microviscosity. Magnesium pidolate at 4.5 g per day (15.8 mmol per day) for four weeks significantly improved insulin action, enhanced total-body and oxidative-glucose metabolism, increased erythrocyte magnesium concentrations and decreased erythrocyte membrane microviscosity.<sup>16</sup>

Similarly, in another double-blind placebo-controlled study of older patients with type 2 DM Paolisso and colleagues administered magnesium (2 g per day) in the diet for four weeks. Magnesium treatment significantly increased plasma and erythrocyte magnesium levels, as well as increased the insulin response and glucose disappearance following a pulse of glucose. During the euglycemic-hyperglycemic glucose-clamp testing in these subjects, those who received chronic magnesium therapy withstood a significantly greater glucose infusion rate. These changes correlated well with the increases in erythrocyte magnesium. Chronic magnesium treatment also significantly decreased the resting plasma glucose levels in these patients with type 2 DM.<sup>17</sup>

Magnesium deficiency has been shown to produce insulin resistance in healthy human subjects. In one study by Nadler and colleagues, lean non-diabetic subjects receiving a low-dose magnesium liquid diet (<0.5 mmol per day) for three weeks, had a significant reduction in intracellular free magnesium in erythrocytes ( $186 \pm 10$  to  $127 \pm 9$  mM) and serum magnesium levels ( $0.78 \pm 0.08$  to  $0.53 \pm 0.08$  mmol/L).<sup>18</sup> However, serum sodium, calcium and potassium were unchanged. An intravenous glucose tolerance test revealed significantly reduced tolerance on the Insulin Sensitivity Index when patients received the low-dose magnesium treatment compared with when they were magnesium replete. In this study, magnesium deficiency also led to increased urinary thromboxane levels and enhanced aldosterone-secreting effects of angiotensin II. The changes on both of these observed indices probably reflect increased activity of processes that can contribute to the underlying pathological changes associated with microvascular and macrovascular damage, therefore, the authors suggest that magnesium deficiency may be a common factor in both insulin resistance and vascular diseases.

A recent human, placebo-controlled study by deValk and colleagues reported the effects of supplemental magnesium (15 mmol per day for three months) in 50 type 2 DM patients requiring insulin. While plasma magnesium and urinary magnesium excretion increased with magnesium therapy, other parameters measured (HbA<sub>1c</sub>, blood glucose, lipids) did not change. There was, however, a slight reduction in diastolic blood pressure in the patients who experienced increased plasma magnesium.<sup>19</sup> Although individuals with compromised magnesium status have reported reduced insulin

release, most of the focus on magnesium supplementation for DM involves preventing long-term complications. Magnesium deficiency has been associated with hypertension, dyslipidemia and retinopathy, all common to DM.<sup>20</sup>

## Magnesium and Diabetic Complications

It is estimated that less than 10% of DM patients die from acute problems associated with the disease such as diabetic ketoacidosis or hypoglycemia. The greatest morbidity and mortality result from long-term complications.

These long-term complications are believed to develop when cells and cellular components are chronically exposed to elevated glucose levels, as seen in poorly controlled DM. The non-enzymatic glycosylation of proteins and the accumulation of polyols (e.g., sorbitol) results in the formation of advanced glycation end products and ultimately cell damage. Hyperlipidemia and hypertension are examples of macrovascular complications associated with DM. The microvascular complications include neuropathies, retinopathy and nephropathy.

The association between magnesium deficiency and the risk of developing diabetic retinopathy was first suggested in 1978.<sup>21</sup> Approximately 75% of patients with type 1 DM will develop some degree of retinopathy after 15 years of diabetic symptoms. In the most extensive study to date, Hartwal and colleagues examined 100 patients with type 2 DM and compared them with 100 controls without DM.<sup>22</sup> Of the DM patients, 40% had no retinopathy, 40% had non-proliferative retinopathy and 20% had proliferative retinopathy, the most serious form (see Table I). When compared with controls, the DM patients had significantly lower serum magnesium levels. Of the DM pa-

**Table 1****Diabetic Retinopathy and Serum Magnesium**

GROUP	N	Serum Magnesium (mmol/L)
Control	100	1.04 ± 0.00
Diabetics—no retinopathy	40	0.88 ± 0.07*
Diabetics—retinopathy (non-proliferative)	40	0.77 ± 0.07*
Diabetics—retinopathy (proliferative)	20	0.66 ± 0.04*

\* Significantly different from control. Adapted from Hartwal, et al.<sup>22</sup>

tients, serum magnesium levels were lower in those patients with retinopathy than those without retinopathy. The lowest serum magnesium levels were observed in those patients with proliferative retinopathy. Although researchers have yet to establish a definitive mechanism underlying the association between magnesium deficit and retinopathy, the compromised insulin release and consequent cellular damage may contribute to disease progression as a result of chronic dysfunction of glucose homeostasis.

### Skeletal Muscle Cramps

Numerous electrolyte disturbances are known to adversely affect normal skeletal muscle function. Of these, hypomagnesemia-induced muscle cramps appear to be especially bothersome to DM patients. The nocturnal leg cramps disrupt sleep causing excessive fatigue and further reducing quality of life for DM patients. Magnesium therapy reportedly alleviates cramps with a number of underlying causes.

Hypomagnesemia patients with early-onset type I DM who complained of nocturnal leg cramps were studied for the ability of magnesium aspartate hydrochloride to reduce symptoms. In this study Bachem and colleagues noted

a complete elimination of cramps in 20 of 24 patients after just a few days of magnesium therapy, (5mg/kg/day, Mg aspartate hydrochloride p.o.). Although the remaining subjects continued to experience some leg cramps, their intensity and frequency was

markedly decreased.<sup>23</sup> Magnesium therapy has also effectively treated leg cramps in patients without DM, even when serum magnesium level appear normal.<sup>24</sup> Magnesium therapy should be considered for DM patients with leg cramps when their renal function is adequate.

### Magnesium Basics—Pharmacokinetics

Total body magnesium averages 20 to 28g with most (65%) located in bone. Of this amount, only 30% is exchangeable and the rest is tightly sequestered in the bone matrix. Intracellular magnesium constitutes approximately 34% of the total, with only 1% located in the extracellular fluid. While normal serum values range from 0.8 to 1.2 mmol/L (1.4 to 2.0 mEq/L), serum magnesium measurements, although routinely done, may not always accurately reflect intracellular levels. Individuals may have serum magnesium levels well within the normal range and yet be total body magnesium deficient. An accurate magnesium deficiency diagnosis, especially the chronic latent variety, can be difficult to make.<sup>25</sup>

The small intestine absorbs most of the dietary magnesium. Typically, about 35 to 60%

of an orally delivered magnesium load is absorbed, but this depends partly upon the individual's current magnesium status. The transport mechanism across the intestinal wall is believed to be passive diffusion or facilitated transport. There does not appear to be active magnesium transport in the small intestine, nor is the colon believed to absorb a significant amount of magnesium. Serum magnesium levels increase as a result of oral magnesium supplementation with one of the many salts available including the amino acid chelates (aspartate HCl), carbonate, chloride, gluconate and oxide. Some studies have demonstrated differences in the bioavailability of the various salts in humans and experimental animals. Research has shown aspartate HCl currently has the greatest bioavailability.<sup>26,27</sup>

Within the serum, magnesium is generally found in three distinct fractions: ionized magnesium (60%), protein-bound magnesium (34%) and complexed magnesium (6%). Within cells, only 1 to 2% of the magnesium is free in the ionized form. The largest contributor to the protein-bound magnesium in serum is albumin, although a number of other proteins do contribute to magnesium binding.

Small amounts of magnesium are excreted in saliva and breast milk, but the body regulates magnesium predominantly by altering its excretion via the kidneys. Ionized magnesium is freely filtered at the glomerulus and reabsorption takes place within the thick segment of the ascending limb of the loop of Henle (70%), the proximal tubule (15%) and the distal tubule (10%). A number of hormones acting on the distal tubule—including various steroids, glucagon, vasopressin, parathyroid hormone and calcitonin—are likely to be involved in controlling magnesium reabsorption, which

attempts to maintain magnesium homeostasis. Recent evidence suggests that the cells within the distal tubule, and possibly the thick ascending limb of the loop of Henle, are capable of adapting to magnesium and calcium availability through receptors that sense the concentration of these cations. Thus, when magnesium status is suboptimal, these receptors sense the need for magnesium retention and cause more reabsorption.

## Drugs That Can Produce Magnesium Deficit

There are a number of clinically useful drugs that can trigger magnesium loss largely because of their action on the kidneys (see Table 2).<sup>28</sup> Important examples include corticosteroids, cyclosporine, digoxin, ethacrynic acid, ethanol, furosemide, methotrexate, oral contraceptives, tetracyclines and the thiazide diuretics. Additionally, laxative abuse can cause magnesium deficiency by preventing intestinal absorption and enhancing gastrointestinal loss. Because DM patients may either chronically or intermittently use some of these drugs, health care providers should pay special attention to the patient's magnesium status.

**Table 2**

### Drugs Known to Deplete Magnesium

Benzthiazide	Ethacrynic acid
Bumetanide	Furosemide
Cholestyramine	Minocycline
Corticosteroids	Penicillamine
Diethylstilbesterol	Quinestrol
Digoxin	Thiazide diuretics
Estrogens	

*Adapted from Pelton, et al.<sup>26</sup>*

Magnesium deficiency is also seen in critically ill patients. In such acute situations, assuming renal function is adequate, aggressive repletion with intravenous magnesium sulfate should be undertaken immediately to prevent serious cardiac arrhythmias and metabolic disturbances. For magnesium repletion, give 12 mg/kg of elemental magnesium intravenously during a 24-hour period during the first day, followed by 6 mg/kg on days two through five. Serum magnesium levels should be monitored daily to avoid hypermagnesemia. Many patients with hypomagnesemia will also be hypokalemic, so it may be necessary to add potassium chloride as well.

## Magnesium Toxicity

Magnesium has a very high therapeutic index. The most common adverse effect associated with oral supplemental magnesium administration is diarrhea. Toxicity from hypermagnesemia is usually only seen in those patients with significant renal impairment who have ingested excessive amounts of magnesium-containing products (e.g., laxatives, cathartics). At magnesium serum levels of 1.5 to 2.5 mmol/L (3 to 5 mEq/L) nausea, vomiting, bradycardia and hypotension can occur. As serum levels approach 2.5 to 5.0 mmol/L (5 to 10 mEq/L) hyporeflexia, EEG abnormalities and generalized central nervous system depression can occur. At concentrations greater than 5 mmol/L (10 mEq/L) severe respiratory depression, coma and asystolic arrest may occur. Many of magnesium's actions at therapeutic concentrations, as well as at toxic concentrations, are caused by the mineral's ability to act at calcium channels. Magnesium can be classified as an endogenous calcium-channel blocker. Treating hypermagnesemia

typically involves stopping magnesium administration and starting calcium.

There is documented evidence that magnesium interacts with neuromuscular blocking agents and central nervous system depressants (e.g., opioids, general anesthetics and barbiturates). However, in the absence of significant renal dysfunction, the most common adverse effects observed with magnesium supplementation involve its laxative effects. Clinicians may use this observation to determine appropriate dosing. A patient is usually started on a low magnesium dose and that dose is gradually increased. If diarrhea occurs, adjust down the dose.

Magnesium is clinically useful for treating a number of disorders (see Table 3). In addition to DM, magnesium has been used as an antiarrhythmic agent, an antihypertensive agent and to retard uterine contractions when beta-adrenoceptor agonists are contraindicated. Additionally, magnesium has been used to treat asthma, headaches and barium poisoning.

## Daily Magnesium Requirements

The U.S. Recommended Dietary Allowance (RDA) and Adequate Intake (AI) for magnesium varies with age and physiological status

**Table 3**

### Other Therapeutic Uses of Magnesium

Arrhythmias (especially <i>torsades de pointes</i> )	Epilepsy Headache Hypertension and cardiovascular disease
Asthma	Peptic Ulcer Disease
Barium intoxication	Uterine relaxation
Constipation	

Adapted from Pelton, et al.<sup>26</sup>

(see Table 4). For adults, the average daily intake should approach 5 mg/kg body weight. Men older than 31 years have the highest requirement (420 mg daily), while the corresponding value for women in that age group is 320 mg daily. Women between 14 and 18 years require 360 mg per day. Pregnancy increases the requirement to 400 mg per day for those younger than 18 years and 350 to 360 mg per day for those older than 18. Similarly, lactation increases the values to 310 to 360 mg daily. Most studies have demonstrated that the average magnesium intake is approximately 20 to 25% below the RDA. Results of other studies suggest that 25 to 50% of the U.S. population have suboptimal dietary magnesium intake.

Many of the foods we eat, whether of animal or plant origin, contain bioavailable magnesium. Some foods with a generally desirable

magnesium content include green leafy vegetables, grains, various nuts (almonds, soy), shrimp, various fish (bluefish, cod, flounder, herring, mackerel, swordfish), wheat germ and chocolate. Because some of the best dietary sources of magnesium are not the most appropriate food choices for DM patients because of the caloric or fat content (e.g., chocolate, nuts), supplementing with one of the available magnesium salts may be the easiest way to insure adequate magnesium intake.

Although the U.S. RDA does not include a greater magnesium intake level for DM patients, supplementing with magnesium may be beneficial considering their tendency to excrete excessive urinary magnesium each day. Numerous magnesium salts are available for use as dietary supplements.

**Table 4**

**Recommended Dietary Allowance (RDA)  
for Magnesium**

Category	Age (years)	Mg (mg/day)
Infants	0–0.5	30*
	0.5–1	75*
Children	1–3	80
	4–8	130
Males	9–13	240
	14–18	410
	19–30	400
	>30	420
Females	9–13	240
	14–18	360
	19–30	310
	>30	320
Pregnancy (Lactation)	<18	400 (360)
	19–30	350 (310)
	31–50	360 (320)

\* Values represent the Adequate Intake (AI) because an RDA has not been established.

## Recommendations and Conclusions

Early studies demonstrated an inverse relationship between plasma magnesium levels and fasting blood-glucose levels in patients with DM. Magnesium deficiency decreases insulin sensitivity via an alteration of the insulin-receptor associated tyrosine kinase, while supplementation with magnesium has been shown to benefit those with type 2 DM. Monitoring the magnesium status of DM patients is important and should be part of their comprehensive therapy. However, because such a small percentage of the total-body magnesium is present in the compartment typically sampled (the plasma or serum), diagnosing magnesium deficiency can be difficult. Studies have demonstrated that despite a normal plasma or serum magnesium level, patients still may be deficient.

Magnesium deficiency can be treated in a number of ways. Diet alone is usually not a practical approach because many of the foods rich in magnesium (such as peanuts, soy beans, cashews, chocolate, dried fruits and shrimp) should not be consumed in large quantities by DM patients because of the high caloric and lipid contents of these foods. Supplemental magnesium is the better choice in this case. Oral magnesium products should be taken with meals to minimize the likelihood of diarrhea. The magnesium salts available for oral use include the amino acid chelates (e.g., aspartate HCl), carbonate, chloride, gluconate and oxide. Some studies have demonstrated significant differences in the bioavailability of the various salts in humans and experimental animals with the aspartate HCl having the greatest absorption and bioavailability.<sup>25,26</sup> Magnesium aspartate HCl has also been reported

to cause less diarrhea than many of the other available magnesium supplements.

Supplementation with magnesium is obviously required for patients with low serum levels. Many clinicians will also routinely recommend magnesium supplements even when serum levels are within the normal range because the diabetic state encourages elimination of magnesium, and because supplementation with this mineral is quite safe.

## References

1. Clark MJ, et al. Diabetes guidelines: a summary and comparison of the recommendations of the American Diabetes Association, Veterans Health Administration, and the American Association of Clinical Endocrinologists. *Clin Therap* 2000;22:899-910.
2. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1997;20:1183-214.
3. Stutzman FL, Amatuzio DS. Blood and serum magnesium in portal cirrhosis and diabetes mellitus. *J Lab Clin Med* 1952;41:215.
4. McNair P, et al. Renal hypomagnesaemia in human diabetes mellitus: its relation to glucose homeostasis. *Eur J Clin Invest* 1982;12:81-5.
5. Ma J, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. *J Clin Epidemiol* 1995;48:927-40.
6. Sasaki S, et al. Abnormal magnesium status in patients with cardiovascular disease. *Clin Sci* 2000;98:175-81.
7. Khan LA, et al. Serum and urinary magnesium in young diabetic subjects in Bangladesh. *Am J Clin Nutr* 1999;69:70-3.
8. Foster H. Diabetes mellitus and low environmental magnesium levels. *Lancet* 1987;2:633.
9. Yang CY, et al. Magnesium in drinking water and the risk of death from diabetes mellitus. *Magnesium Res* 1999;12:131-7.
10. Lefebvre PJ, Scheen AJ. Improving the action of insulin. *Clin Invest Med* 1995;18:340-7.
11. Suarez A, et al. Decreased insulin sensitivity in skeletal muscle of hypomagnesemic rats. *Diabetologia* 1993;36(Suppl 1):A82.
12. Laughlin MR, Thompson D. The regulatory role for magnesium in glycolytic flux of the human erythrocyte. *J Biol Chem* 1996;271:28977-83.
13. Balon TW, et al. Magnesium supplementation reduces development of diabetes in a rat model. *Am J Physiol* 1995;269:E745-52.
14. Yajnik CS, et al. Fasting plasma magnesium concentrations and glucose disposal in diabetes. *Br Med J* 1993;288:1032-4.
15. Paolisso G, et al. Impaired insulin-induced erythrocyte magnesium accumulation is correlated to impaired insulin-mediated glucose disposal in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia* 1988;31:910-5.
16. Paolisso G, et al. Daily magnesium supplements improve glucose handling in elderly subjects. *Am J Clin Nutr* 1992;55:1161-7.
17. Paolisso G, et al. Improved insulin response and action by chronic magnesium administration in aged NIDDM subjects. *Diabetes Care* 1989;12:265-9.
18. Nadler JL, et al. Magnesium deficiency produces insulin resistance and increased thromboxane synthesis. *Hypertension* 1993;21:1024-9.
19. DeValk HW, et al. Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med* 1998;15:503-7.
20. Seelig M. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations—magnesium and chloride loss in refractory potassium repletion. *Am J Cardiol* 1989;63:4G-21G.
21. McNair P, et al. Hypomagnesemia, a risk factor in diabetic retinopathy. *Diabetes* 1978;27:1075-7.
22. Hatwal A, et al. Association of hypomagnesemia with diabetic retinopathy. *Acta Ophthalmol* 1989; 67(Copenh):714-6.
23. Bachem MG, et al. Efficacy of oral magnesium supplementation in type 1 diabetics with nocturnal leg cramps. *Magnesium Bull* 1986;8:280-3.
24. Haringer E. Are nocturnal cramps in the calf due to magnesium deficiency? Normal serum magnesium concentrations do not rule out the presence of abnormally low intracellular magnesium levels. *Arztliche Praxis* 1981;77:2653-4.
25. Gums JG. Clinical significance of magnesium: a review. *Drug Intell Clin Pharm* 1987;21:240-6.
26. Muhlbauer B, et al. Magnesium-L-aspartate-HCl and magnesium-oxide: bioavailability in healthy volunteers. *Eur J Clin Pharmacol* 1991;40:437-8.
27. Classen HG, et al. Comparative animal studies on the absorption of magnesium in sulfate, chloride, aspartate and aspartate hydrochloride form from the gastrointestinal tract. *Arzneim-Forsch (Drug Res)* 1973;23:267-71.
28. Pelton R, et al. Drug-induced nutrient depletion handbook, 1999-2000. San Diego(CA): Natural Health Resources; 2000.

## Magnesium and Diabetes Mellitus

### Continuing Education Module Questions

1. The U.S. Recommended Dietary Allowance (RDA) for magnesium for a male aged 31 years or older:
  - a. 75 mg
  - b. 1,200 mg
  - c. 5 mg/kg
  - d. 420 mg/kg
2. Therapeutically, magnesium can be used:
  - a. as a uterine relaxant
  - b. as an antiarrhythmic
  - c. for barium intoxication
  - d. all of the above
3. Which agents are known to enhance renal magnesium excretion:
  - a. cephalosporin antibiotics
  - b. testosterone
  - c. corticosteroids
  - d. HMG CoA reductase inhibitors
4. In patients with diabetes mellitus, the most compelling data to date supports an association between hypomagnesemia and:
  - a. the degree of urinary glucose spillage
  - b. HbA<sub>1c</sub> levels
  - c. severity of diabetic complications such as retinopathy
  - d. blood glucose levels
5. The most common adverse effect associated with magnesium supplementation in patients with diabetes mellitus is:
  - a. headache
  - b. arrhythmias
  - c. muscle pain
  - d. diarrhea
6. Normal serum magnesium levels are:
  - a. 0.1–0.3 mmol/L
  - b. 0.4–0.6 mmol/L
  - c. 0.8–1.2 mmol/L
  - d. 2.0–4.0 mmol/L
7. In patients with diabetes mellitus, magnesium deficiency:
  - a. increases insulin release
  - b. decreases insulin resistance
  - c. is commonly observed
  - d. leads to hypercalcemia
8. Numerous studies have demonstrated that the level of magnesium in the drinking water of patients with diabetes mellitus is inversely correlated with:
  - a. serum potassium
  - b. diabetes mellitus-related mortality
  - c. tyrosine kinase activity
  - d. forced expiratory volume per minute (FEV<sub>1</sub>)
9. Most of the body's magnesium is stored in the:
  - a. blood
  - b. bone
  - c. muscle
  - d. pancreas
10. Which magnesium salts, when administered orally, reportedly have greater bioavailability and fewer gastrointestinal effects:
  - a. aspartate hydrochloride
  - b. carbonate
  - c. chloride
  - d. oxide

## Answer Sheet and Post Test Instructions

**Massachusetts College of Pharmacy and Health Sciences** will grant 1 contact hours (0.1 CEUs) to pharmacists who read this supplement, correctly answer 70% of the accompanying questions and submit the completed examination to Massachusetts College of Pharmacy and Health Sciences.

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### Diabetes Mellitus and Magnesium: Unlikely Partners

Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ Zip Code \_\_\_\_\_ Telephone \_\_\_\_\_

State & License Number \_\_\_\_\_ Pharmacist \_\_\_\_\_ Physician \_\_\_\_\_ Other \_\_\_\_\_

Please indicate your exam response by circling only **ONE** answer for each.

- |            |            |            |             |
|------------|------------|------------|-------------|
| 1. A B C D | 4. A B C D | 7. A B C D | 10. A B C D |
| 2. A B C D | 5. A B C D | 8. A B C D |             |
| 3. A B C D | 6. A B C D | 9. A B C D |             |

**Program Evaluation:**

Overall quality:

**Agree**

(Excellent)

**Disagree**

(Poor)

1            2            3            4            5

Objectives:

(All met)

(None met)

1            2            3            4            5

Relevance to practice:

(Extremely relevant)

(Not relevant)

1            2            3            4            5

It took me \_\_\_\_\_ hours \_\_\_\_\_ min to read this article and complete the exam.

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